

**Remarks**

The Office action mailed June 15, 2005, has been reviewed and carefully considered. Applicants thank examiners Cordero Garcia and Tate for the courtesy extended during the telephone interviews of August 31, 2005, and November 16, 2005. Claims 15 and 28 have been amended to correct an inadvertent typographical error. Non-elected claim 23 has been canceled without prejudice towards filing a divisional application. Claim 27 has been canceled. Non-elected claim 24 has been amended to include the features of claim 1 for purposes of rejoinder. Claim 18 has been amended to revise the formula. Support for the amendment to claim 18 is found in the specification, for example, in the formulae found on pages 11 and 36. Claim 21 has been amended for purposes of clarification. New claims 41-94 have been added. Entry of these amendments is respectfully requested.

Support for claims 41, 55, 58 and 59 is found in the specification, for example, at page 22, line 23, original claim 11, and page 92, lines 23-35. Support for claim 42 is found in the specification, for example, at page 22, line 23, original claim 11, page 92, lines 23-35 and page 20, lines 28-29. Support for claims 43-46, 54, 60 and 72-75 is found in the specification, for example, at page 20, lines 28-29. Support for claim 47 is found in the specification, for example, at page 92, line 33. Support for claim 48 and 61 is found in the specification, for example, at page 44, lines 13-28 and page 93, line 4. Support for claims 49, 56, 57, 62 and 63-70 is found throughout the specification. Support for claims 50 and 51 is found in the specification, for example, at page 44, line 30 – page 45, line 17 and page 96, lines 9-13. Support for claim 52 is found in the specification, for example, in original claim 11. Support for claim 53 is found in the specification, for example, at page 35, lines 18-30. Support for claim 71 is found in the specification, for example, at page 46, lines 13-28. Support for claims 76-80 is found in the specification, for example, at page 20, lines 28-29. Support for claim 81 is found in the specification, for example, at page 36, lines 22-23 and page 38, lines 15-16. Support for claims 82 is found in the specification, for example, at page 38, lines 7-16. Support for claims 83-86 is found in the specification, for example, at page 37, lines 1-20. Support for claim 87 is found in the specification, for example, at page 37, lines 21-28 and original claim 21. Support for claim 88 is found in the specification, for example, at page 46, lines 14-24. Support for claim 89 is found in the specification, for example, at page 36, lines 18-19. Support for claim 90 is found in

the specification, for example, at page 37, lines 21-28, page 36, lines 18-20, page 44, line 30 – page 45, line 3; page 46, line 9 – page 47, line 24 and original claim 21. Support for claims 91 and 92 is found in the specification, for example, at page 19, lines 24-25 and page 20, lines 8-10. Support for claim 93 is found in the specification, for example, at page 92, lines 23-24. Support for claim 94 is found in original claim 27, which was withdrawn and is now canceled.

#### Restriction Requirement

As discussed during the August 31, 2005 interview, applicants are entitled to rejoinder of non-elected claims 22 and 94 (original claim 27). In addition, non-elected claim 24 has been amended to include the features of claim 1 for purposes of rejoinder. Thus, non-elected claims 22 and 24-26 and 94 should be re-joined with the elected claims and be allowed to issue in the present application.

#### Rejections under 35 U.S.C. §103

Claims 1-21 and 28-40 have been rejected under 35 U.S.C. §103 over Deadman et al. (J Med Chem 1995) in view of Skordalakes et al. (J Am Chem 1997). Deadman et al. discloses various boropeptide esters. However, Deadman et al. does not describe any salt of an organoboronic acid, much less a salt of a multivalent metal as presently claimed. Skordalakes et al. purports to disclose two boronic acids, designated compound 1 and compound 2. Skordalakes et al. also does not describe any salt of an organoboronic acid, much less a salt of a multivalent metal as presently claimed. Even assuming *arguendo* that there would have been motivation to combine Deadman et al. and Skordalakes et al., the combination would not have resulted in the salt recited in claim 1 since neither Deadman et al. nor Skordalakes et al. describe any salt. Hence, a *prima facie* case of obviousness has not been established and the 35 U.S.C. §103 rejection over Deadman et al. combined with Skordalakes et al. must be withdrawn.

Claims 1-21 and 28-40 also have been rejected under 35 U.S.C. §103 over Claeson et al. (Biochem J 1993) in view of Skordalakes et al. (J Am Chem 1997). Claeson et al., similar to Deadman et al., discloses a boropeptide pinanediol ester. Claeson et al. also does not describe any salt of an organoboronic acid, much less a salt of a multivalent metal as presently claimed.

Skordalakes et al. is discussed above. Even assuming *arguendo* that there would have been motivation to combine Claeson et al. and Skordalakes et al., the combination would not have resulted in the salt recited in claim 1 since neither Claeson et al. nor Skordalakes et al. describe any salt. Hence, a *prima facie* case of obviousness has not been established and the 35 U.S.C. §103 rejection over Claeson et al. combined with Skordalakes et al. must be withdrawn.

It is asserted in the Office action that it would have been obvious “to adjust particular conventional working conditions” to arrive at the claimed salts and that “[t]hese types of adjustments are deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.” However, no references were cited in the Office action supporting these assertions. (See MPEP §2144.03).

During the telephone interview of August 31, 2005, the PTO directed the applicants’ attorney’s attention to a document (Bastin et al., “Salt Section and Optimisation Procedures for Pharmaceutical New Chemical Entities” Organic Process Research & Development 2000, 4, 427-435) that was not relied upon for the rejections in the Office action. Bastin et al. generally discusses various parameters that may influence selection of an appropriate salt form for a biologically active agent that may be suitable for further development. In contrast to the presently claimed salt, Bastin et al. does not discuss the chemistry of boronic acids or attribute any advantage to salts of boronic acids or multivalent metals. Boronic acids have a chemistry distinct from that of carboxylic and other acids (see, for example, the present specification at page 4, line 33 to page 5, line 13 and page 6, lines 1-24) and the skilled person would not look to a treatise discussing other acids for guidance on boronic acids. For this reason alone, any asserted combination of Bastin et al. with either Deadman et al. or Claeson et al. would not have resulted in the presently claimed salts.

In addition, Bastin et al. would not have motivated one of ordinary skill in the art to modify the compounds of either Deadman et al. or Claeson et al. The work reported in the Deadman et al. paper focused on trying various modifications of the peptide side chains (particularly at the P1 site) as opposed to modification of the boron-containing moiety (see structures shown in Tables 1-3 wherein R, R<sup>1</sup>, and R<sup>2</sup> substituents are varied). In other words, all the structures shown in Deadman et al. have the same type of boron-containing moiety, namely an ester. The structure-activity relationship discussion in Deadman et al. also focuses on the side chain modifications made in the series of compounds. It follows that there would have been no

suggestion in Deadman et al. to modify the boron-containing moiety by making a salt thereof. Claeson et al. discloses that a neutral methoxypropyl side chain on a boropeptide pinacol ester provided thrombin inhibition activity. Claeson et al. discloses an ester and does not attach any significance to the identity (whether free acid, ester or otherwise) of the boronyl moiety of the compound, and thus certainly would not have suggested manipulation of the boronyl moiety. Furthermore, since Bastin et al. makes no mention of any organoboronic compounds, a skilled artisan would not have been prompted by Bastin et al. to make salts of organoboronic compounds. Thus, Deadman et al., Claeson et al. and Bastin et al. together would not have suggested making a salt of an organoboronic acid inhibitor.

Double Patenting Rejection

Claims 1-21 and 28-40 have been provisionally rejected for double patenting over claims 28-38 of copending Application No. 11/078,097. Claims 1-21 and 28-40 also have been provisionally rejected for double patenting over claims 1-24 and 50-58 of copending Application No. 10/659,178 (applicants note that currently there are no claims 50-58 in the '178 application). Applicants thank examiner Cordero Garcia for the courtesy extended during the telephone interview of November 16, 2005, regarding the provisional double patenting rejection.

As agreed during the November 16<sup>th</sup> interview, since the claims in the '097 and '178 application have not yet issued or even been allowed the provisional double patenting rejections will be withdrawn once the present application (10/659,179) is in condition for allowance.

Statement of the Substance of Interviews

Applicants confirm that the Interview Summary mailed by the examiner on September 9, 2005, accurately reflects the substance of the interview conducted on August 31, 2005. During the interview, Applicants' representative presented the arguments against the obviousness rejections as detailed above. The examiner directed the applicants' representative to the Bastin et al. reference, which is now discussed in detail above.

During the November 16, 2005, telephone interview between examiner Cordero Garcia and the undersigned the provisional double patenting rejections were discussed. It was agreed

that the provisional double patenting rejections will be withdrawn once the present application is in condition for allowance since the claims in the '097 and '178 application have not yet issued or even been allowed.

Certified Copies of Foreign Priority Documents

The Office Action Summary indicates that none of the certified copies of the foreign priority documents have been received. Certified copies of the foreign priority documents were submitted at the time of filing the application as indicated on the application transmittal letter, on the stamped postcard accompanying the filing of the application, and as shown in PAIR. Consequently, the next action issued by the PTO in this case should confirm that the certified copies have been received.

It is respectfully submitted that the present application is in condition for allowance (and thus the provisional double patenting rejections should be withdrawn). Should there be any questions regarding this application, examiner Cordero Garcia is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By   
Wayne W. Rupert  
Registration No. 34,420

One World Trade Center, Suite 1600  
121 S.W. Salmon Street  
Portland, Oregon 97204  
Telephone: (503) 595-5300  
Facsimile: (503) 228-9446